



Cardiotonic Drugs

Cardiotonic Drugs they are drugs that stimulate the contractility of the Heart leading to increase efficiency of the Heart.

Points of Lecture:

- ✓ Concept.
- ✓ Classification.
- ✓ Mechanism of Action.
- ✓ Main Pharmacological effects.
 - it depends on: wanted or unwanted effects, in other words, desired and undesired effects.
- ✓ Pharmacokinetics.
- ✓ Clinical uses.
- ✓ Contraindications and Precautions.
- ✓ Treatment of Heart Failure.
 - The compensatory mechanism → Increases progression of HF, if we understand that, we can know the main classes for treatment of HF. The classes, the drugs and some properties of these drugs.

Concept

Cardiotonics (Cardiac stimulation) these are drugs that stimulate the Heart. The stimulation drug can be with increasing oxygen consumption or without need of oxygen consumption. The drugs that increases cardiac action with increasing oxygen consumption are very bad for the failing heart.

Cardiac stimulation drugs like *Theophylline* (Anti-Asthmatic) used for Asthma patients is a bronchodilator and it is also used in COPD patients. It stimulates the heart with increasing oxygen demand (it needs much more oxygen and blood for the Heart) so for the failing heart *Theophylline* is bad, in failing heart there is no pumping efficiency so *Theophylline* will lead to decrease the efficiency in cardiac failure. So cardiac stimulator with increasing oxygen demand are not good for failing heart.

But the drugs that ▲ the contractility directly without increasing oxygen demand they are what we call them *Digitalis*. *Digitalis* the main example is *Digoxin*, it acts directly on the cardiac myocyte and ▲ the cardiac contractility without any demand or ▲ oxygen consumption. So it has a + inotropic effect.

What do we mean by + inotropic effect? ▲ cardiac contractility.

What do we mean by - Inotropic effect? ▼ cardiac contractility.

Which drugs that produce – inotropic effect?

1. Beta blockers.
2. Calcium channel Blockers (e.g. *Verapamil* and *Diltiazem*).

The cardiotonics have + inotropic effect also they have – chronotropic effect (▼ Heart rate) so the action of *Digitalis*, *Digoxin* on heart is mainly ▲ the cardiac contractility in inefficient state → ▲ CO → relieve the symptoms of HF. It is not used for the progression and prolonged survival only used to relieve symptoms of HF.

Digoxin comes from a plant called *Digitalis purpurea*. These plants have the *Digitalis* (*Digoxin*, *Digitoxin* and *Ouabain*).

What do we mean by Heart Failure?

The pumping efficiency of the heart is low that lead to ▼ CO → ▼ Perfusion to all organs → then we have oliguria and ▼ Perfusion and so on.

For the body to compensate this situation, it will make compensatory mechanisms to ▲ CO and ▲ perfusion to all organs.

Three phases in the Pathology of Heart Failure:

1. Volume Expansion → by inhibition of Na⁺ excretion and ▲ Absorption of Na⁺ and water by the kidneys.
2. ▲ Stimulation of SNS → Adrenaline and nor-adrenaline release → Action on Beta and Alpha receptors → ▲ PVR.
3. Stimulation of RAS → it will give Angiotensin II and Aldosterone → Angiotensin II is a Potent Vasoconstriction (more than adrenaline and nor-adrenaline) and aldosterone bind to its receptors in the kidney → ▲ Na⁺ and water reabsorption and ▲ secretion of K⁺ → ▲ Volume expansion, peripheral edema and pulmonary edema (symptoms of HF).

These mechanisms, mainly, Volume expansion, at the beginning is good it will ▲ CO but with continuous time it will lead to ▼ CO. you know when ▲ Volume expansion → ▲ blood returning to the heart → ▲ Preload (End diastolic pressure and increase volume in the heart) that means when ▲ Preload the volume of blood at the beginning of systole is high. When this is continuous for long time it will lead to dilatation of the muscles of the heart → ventricular dilatation or remodeling. This compensatory mechanism after long period it will lead to progression of HF and ▼ CO. RAS and SNS ▲ vasoconstriction so ▲ the ventricular outflow → ▲ Afterload.

So if we want to ▼ afterload we give Vasodilators. Afterload is the end systolic pressure (outflow pumping of blood into arteries). Whenever ▲ PVR the efficiency ▼ so we give vasodilators.

Therefore, uncontrolled and untreated HTN lead, at the end, to HF because it ▲ Afterload. Treatment in RAS we use, RAS inhibitors, e.g. ACE inhibitors, ARBs or vasodilators:

- ✓ Venodilators, expansion of veins → ▼ Preload, ▼ stress on heart, ▼ dilated muscle size → improve function. Nitrites, e.g. Isosorbide dinitrite and Isosorbide mononitrite. When we say venodilators are they completely 100% only relax vein? **No**, they are 90% Venodilators and 10% arteriodilators. The major clinical effect is ▲ dilation of veins ▼ Preload and relax veins.

- ✓ Arteriodilators → relaxation of arteries (e.g. Hydralazine). The problem with arteriodilators, when dilation of arteries (e.g. Aorta and Carotids) occurs the baroreceptors which are sensitive to any dilation sends signals (reflex stimulation). Reflex stimulation means the releases of Nor-adrenaline → action on Beta 1 receptors → ▲ cardiac contractility → Tachycardia. Also increased Na⁺ and water retention → edema.

So what are side effects of *Hydralazine*? Tachycardia and edema.

How to treat these side effects while using *Hydralazine*?

For tachycardia → Beta blockers

Edema → Diuretics.

So *Hydralazine* is not given alone. We give it usually in combination with beta blockers and Diuretics to reverse the side effects. Usually when we have a patient with stroke and we want to treat the ▲ BP we give Hydralazine I.V, Diuretics and beta blockers to block the side effects of *Hydralazine*.

- ✓ Veno+Arteriodilators (e.g. ACE inhibitors and others) → dilation of arteries and veins in balance (there is no reflex tachycardia or edema). Veno+Areteriodilators have no reflex tachycardia or edema as side effects because there is balance. They are 80% Arteriodilator so they are mainly arteriodilators. The Veno+Arteriodilators are used in combination for treatment of HF, the venodilator ▼ Preload and the arteriodilator ▼ Afterload.

The treatment of CHF is by two groups *Hydralazine* (arteriodilator) and Nitrites (venodilator) but treatment of HTN we use only Arteriodilator (*Hydralazine*) or Calcium channel blockers we don't use venodilators for treatment of HTN.

We finished now the compensatory mechanisms and what are the options for treatment of HF:

1. Inhibitors of RAS.
2. Vasodilators.
3. Diuretics (mainly Loop diuretics, thiazides and Spironolactone).

4. Inhibitors of SNS.

Digoxin ▲ cardiac contractility → ▲ CO → ▼ most of these compensatory mechanisms.

Classification:

- ✓ First Class: *Digitalis (Digoxin, Digitoxin and Ouabain)*
- ✓ Second Class: *Phosphodiesterase inhibitors (Amrinone and Milirinone)*
- ✓ Third Class: *Sympathetic Agonists (Dopamine and Dobutamine)*

What is the difference between *Digoxin* and *Digitoxin*?

Digoxin is short and Digitoxin long. There is difference in pharmacokinetics Digoxin has short action, short half-life but Digitoxin has long action, long half-life and high toxicity, therefore in the clinic we use only Digoxin not Digitoxin. Ouabain is not used because used only by parenteral route. The only drug from *Digitalis* used for treatment of CHF is *Digoxin*.

Digitalis is a glycoside, consists of Aglycone + Sugar. Aglycone is used for binding to receptors and the sugar for solubility and absorption.

All these classes of drugs (*Digitalis, PDI, Dopamine and Dobutamine*) are used usually in severe cardiac failure in acute cases (Decompensated HF).

The only one that is used in Chronic HF is *Digoxin* used oral 0.25 mg daily for long time to ▲ the efficiency of the Heart (in 3rd or 4th grade HF).

Mechanism of action

In the Heart we have conducting and contracting tissues. The conducting Tissue is SA node, AV node and Purkinje fibers, they give the alarm for contracting tissue to contract. The normal action potential in the figure:

Mechanism of action of digoxin

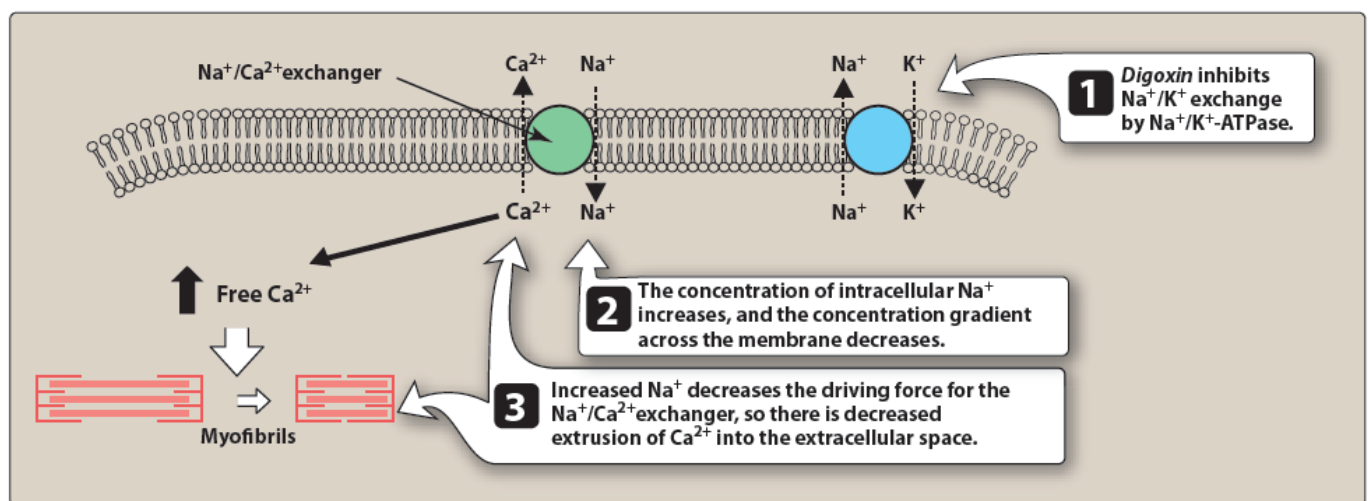
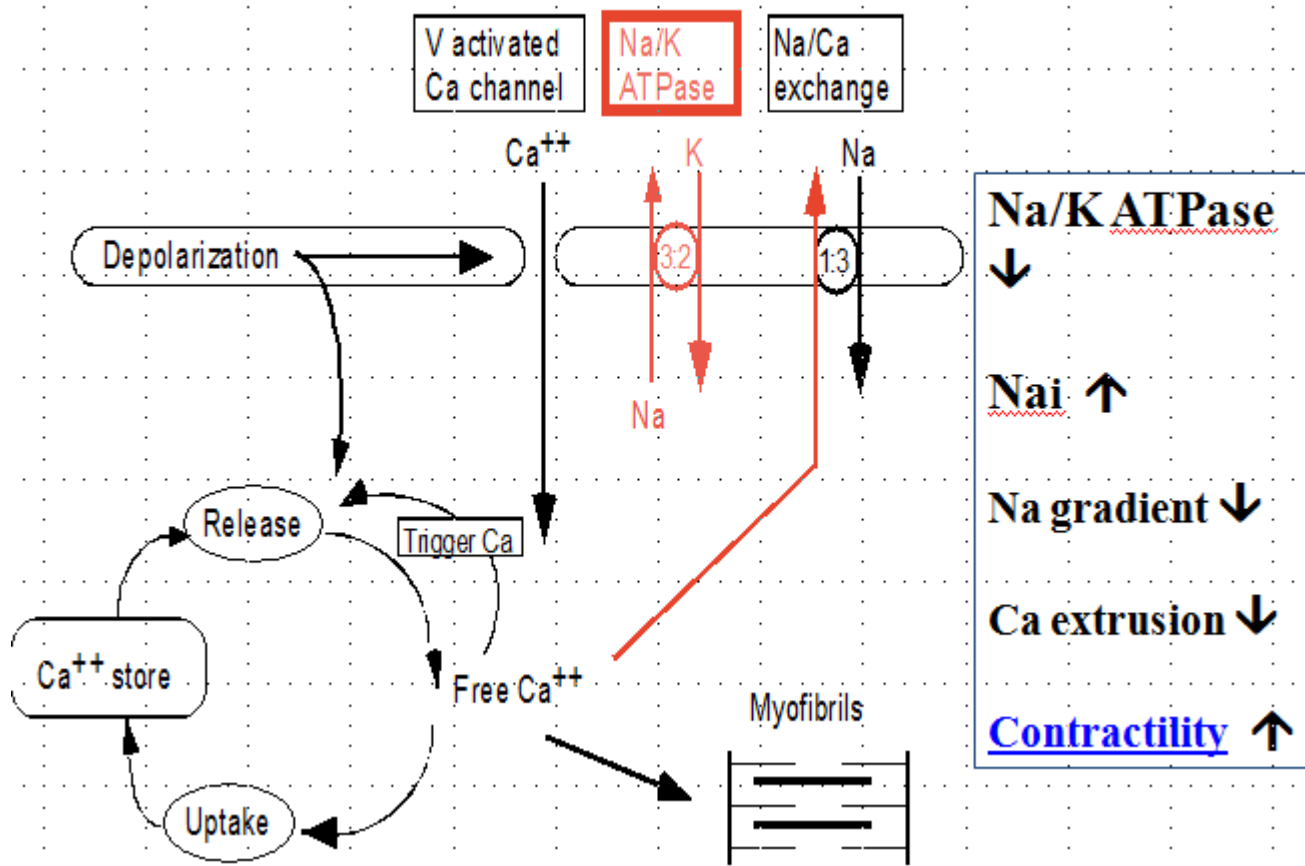


Figure 16.8

Mechanism of action of *digoxin*. ATPase = adenosine triphosphatase.

▲ Na^+ in and then stimulate slow Ca^{2+} in (slow voltage sensitive calcium). the Na^+ enter fast and Ca^{2+} slowly. When Ca^{2+} ▲ inside the cell it stimulates the release of stored calcium in sarcoplasmic reticulum. The influxed calcium and the released calcium → ▲ Ca^{2+} concentration in the cell → coupling of myosin and actin → contraction.

There is a carrier that take Ca^{2+} out and enter Na^{+} (3Na^{+} for 1Ca^{2+}) and this another Ca^{2+} is returned back to the store and then comes to the repolarization.

In repolarization Ca^{2+} gets out and go to the store and Na^{+} enter to have the resting state. After that Na^{+} will $\blacktriangle$ because Na^{+} entered into the cell so will lead to activation of an enzyme called $\text{Na}^{+}\text{K}^{+}\text{ATPase}$, this enzyme will take 3 Na^{+} out and enter K^{+} to the cell and the cell go to the resting state.

The action of Digoxin is by binding to $\text{Na}^{+}\text{K}^{+}\text{ATPase}$ (the site of Action of digoxin lead to inhibition of $\text{Na}^{+}\text{K}^{+}\text{ATPase}$), so what are the consequences of this inhibition?

Another action potential will come $\rightarrow \text{Na}^{+}$ in, Ca^{2+} in, Ca^{2+} out $\rightarrow \blacktriangle \text{Ca}^{2+} \rightarrow$ contraction. After contraction Ca^{2+} returned again and Ca^{2+} out and Na^{+} in $\rightarrow \blacktriangle \text{Na}^{+}$. Na^{+} must go out there is no efflux for Na^{+} because it was blocked by Digoxin so Na^{+} will $\blacktriangle$ in cells. When Na^{+} $\blacktriangle$ in cells, the second action potential will come $\rightarrow \text{Ca}^{2+}$ in $\rightarrow$ release $\text{Ca}^{2+} \rightarrow$ contraction. Here now Ca^{2+} can't go out why because $\blacktriangle \text{Na}^{+}$ concentration cause cancelling of Na^{+} and Ca^{2+} exchange because in order to get Ca^{2+} out, Na^{+} must go outside more and the Na^{+} inside must be low.

Digoxin $\blacktriangle$ contractility of the heart because it $\blacktriangle \text{Ca}^{2+}$ storage and if we $\blacktriangle$ the dose it will cause $\rightarrow$ arrhythmias because $\blacktriangle \text{Ca}^{2+}$ will $\blacktriangle$ the excitability of the cells and will lead to the arrhythmias.

The main toxic effect of *Digoxin* is arrhythmias.

Digoxin has a low therapeutic window so the dose is very important. If the dose $\blacktriangle$ a little it will lead to toxicity so the patient should take Digoxin from the same Manufacturer because Digoxin differs from different manufacturers.

The main molecule that play role in producing action potential in conducting tissue is Ca^{2+} . Na^{+} for contractility. *Digitalis* lead to $\blacktriangle$ conduction and $\blacktriangle$ refractory period $\rightarrow \blacktriangledown$ HR. so it has two effects $\blacktriangledown$ HR and + inotropic effect.

Pharmacological effects

- ✓ Direct Pharmacological effects (on the Heart) → ▲ Contractility and ▼ HR. ▼ HR by two mechanisms:

1. ▲ conduction and ▲ refractory period.
2. Stimulation of Vagal system (action of acetylcholine → action on M2 receptors on SA node → ▼ HR.

The question here why Vagal Action? In mechanism of HF there is ▲ Sympathetic action. If we use *Digoxin* → ▼ Sympathetic action and ▲ Vagal action → ▼ HR.

- ✓ Extra-cardiac Actions of Digoxin:

1. Mild direct vasoconstriction (limited not clinically important).
2. Diuresis in case of CHF → patients with CHF have oliguria and by using *Digoxin* → ▲ CO → ▲ Perfusion in kidneys → Diuresis. Only this occur in patients with CHF not normal persons.
3. CNS → Nausea and Vomiting. If patient is vomiting it is an indication of Toxicity with *Digoxin*. So how we treat this? Stopping Digoxin.

Pharmacokinetics

Q: Make a comparison between *Digoxin* and *Digitoxin*?

Pharmacokinetics		
	<u>Digitoxin</u>	<u>digoxin</u>
1. oral absorption	90-100%	60-80%
2. plasma protein binding	95%	25%
3. Time course of action		
-onset	2 hrs	30 minutes
-peak	6-12 h	2-5 hrs
-duration	2-3 weeks	2-8 days
4. plasma t _{1/2}	5-7 days	40 hrs
5. plasma concentration		
-therapeutic	15-30 ng/ml	0.8-2 ng/ml
-toxic	more than 35 ng/ml	25 ng/ml
6. Daily maintenance dose	0.05-0.2 mg	0.125-0.5 mg
7. Administration	oral	oral, i.v.
8. Metabolism	hepatic	renal

Adverse Reactions:

Nausea, Vomiting and CNS effects. The main toxic effect is Arrhythmia.

Clinical uses

- ✓ CHF in only class III and IV of NYHA.

Table 7.2 The New York Heart Association (NYHA) functional classification of heart failure symptoms

NYHA class	Description
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnoea
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased

From: The Criteria Committee of the New York Heart Association. 1994. *Nomenclature and criteria for diagnosis of diseases of the heart and great vessels*, 9th edn. Boston, MA: Little, Brown & Co, 253–256.

In class III and IV start the production of Aldosterone in heart (local aldosterone). In severe cases lead to Ventricular remodeling, so we give these severe cases Aldosterone antagonists (*Aldactone* or *spironolactone*). Amiloride or Triamterene we don't use them in these cases. Using Aldosterone antagonists (*Aldactone* or *spironolactone*) in CHF patients to improve progression of the disease they inhibit Aldosterone that is responsible for the Ventricular remodeling.

Digoxin is used in CHF when there are symptoms. The maintenance treatment are ACE inhibitors and Diuretics. In the class III and IV of NYHA we add *Digoxin* (severe CHF mainly Left HF because left side depends on contraction and the right depends on filling). Digoxin is contraindicated in right HF.

If a patient comes with HF Class II with Atrial fibrillation and/or arterial flutter, we give him *Digoxin*.

Dosage

- ✓ Slow Digitalization.
- ✓ Rapid Digitalization.

We use in the clinic slow digitalization low dose 0.25 mg/day (Maintenance Dose) for long time, the effect starts after 1 week.

Rapid Digitalization usually by I.V is very serious because it may lead to arrhythmia, not used now.

Drug interactions

- ✓ *Digoxin* and *Diuretics* → the effect of interaction is arrhythmia because Diuretics produce Hypokalemia (Hypokalemia predispose to Digoxin toxicity, because both of the bind to Na⁺K ATPase). Hyperkalemia or Hypokalemia both can lead to arrhythmias.
- ✓ *Digoxin* and *Ca²⁺* → Digoxin lead to ▲ intracellular Ca²⁺. If we give Ca²⁺ it will lead to → arrhythmia because of synergism.
- ✓ *Digoxin* and *Quinidine* (Anti-Arrhythmic) → Displacement of Digoxin from plasma binding sites → Digoxin toxicity.
- ✓ *Digoxin* and *Metoclopramide* (antiemetic) → ▲ excretion of Digoxin, ▼ absorption of Digoxin, ▼ effect of Digoxin.
- ✓ *Digoxin* and *Propranolol* → non selective Beta blockers are contraindicated in HF because it causes opposed action. Digoxin makes contraction and propranolol causes Bradycardia so it will cause cancelling of the action. It is possible for the selective beta blockers in low doses and not all the selective only those that clinical studies have shown to ▼ Mortality and morbidity (*Metoprolol, Bisoprolol, Carvedilol and Nebivolol*) these drugs they allowed them for the treatment of HF before 20 years at low doses only, if we use high or normal doses of them it will cause Bradycardia. This causes confusion some will say beta blockers are contraindicated in HF he relied on Propranolol, another one will say propranolol is indicated for HF he relied on selective betablockers. So always when we talk about HF we talk about the drugs (selective or non-selective betablockers). Non selective betablockers are contraindicated and B1 selective are indicated because they have small effects at low doses in stable state HF it has shown reduction in mortality.

HF patient given ACE inhibitors and Diuretics his symptoms ▼ stage II become stable so we give him very slow dose of selective betablockers (*Metoprolol, Bisoprolol, Carvedilol and Nebivolol*) to ▼ Morbidity and mortality. Start low and go slow that mean start at low dose and when to increase after 2-3 weeks go slowly the dose is 0.125 mg.

Precautions

Read it in PowerPoint.

Q: Patient with Hypokalemia do we give him *Digoxin*?

No.

Now we come to the site of Drug action in the Compensatory mechanisms:

- ✓ Treatment of Volume Expansion → Diuretics.
- ✓ RAS → ACE inhibitors and ARBs
- ✓ SNS → Beta blockers
- ✓ Aldosterone → spironolactone
- ✓ Vasoconstriction → Arteriodilator (*Hydralazine*)
- ✓ Venous return → Venodilators (*Nitrates*)

The first group of Goals of treatment of HF:

- ✓ Drugs that are used as treatment (decrease side effect and improve the condition).
- ✓ Drugs that prolong survival (ACE inhibitors, selective Beta blockers) and Also Aldosterone antagonists because aldosterone is produced in Stage III and IV NYHA so it may prolong survival.

Why angiotensin II is very bad it has 7 things to do it has very serious action:

1. First it is a potent vasoconstrictor.
2. Stimulate release of adrenaline → ▲ PVR.
3. Kidney damage due to Vasoconstriction of Glomerular arterioles → ▼ Filtration.

The patient who uses ACE inhibitors for long time may lead to kidney insufficiency. If we have contraindication of ACE inhibitors, what we will use instead of it? We will use vasodilators because it will cause dilation of arteries and venules (Combination of Nitrates and Hydralazine).

4. Mitogenic effect → hypertrophy due to volume overload.

The questions in PowerPoint you will find the answers in page 521 Tripathi read it very important

Read from Tripathi from 512 – 525. Page 521 for seminar discussion and question.

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هذه الملخصات هي عبارة عن اجتهاد شخصي لمجموعة من طلاب الطب البشري/ عدن معتمدين على ما تم محاضراته او قراءته.. وقد تفيد البعض منكم. وللعلم ليس لها أي علاقة مباشرة بأي عضو من أعضاء الهيئة التعليمية في الكلية. زملائنا الأعزاء إن أصبنا فمن الله، وإن اخطأنا فمن أنفسنا ومن الشيطان. نبقي بشرا نخطئ ونصيب لذا يرجى الاشعار في حالة وجود أي ملاحظات عبر ايميل الجروب او في جروبنا على الفيس بوك
(sharencare@outlook.com)